UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,854	06/21/2001	Krys Bankiewicz	0800-0014.01	9216

31048 7590 10/16/2003

ROBINS & PASTERNAK LLP
1731 EMBARCADERO ROAD
SUITE 230
PALO ALTO, CA 94303

EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,854	BANKIEWICZ ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment and declaration by Drs. Bankiewicz and Cunningham filed 8-1-03 have been entered. Claims 21, 22 and 25 have been amended. Claims 21-25 are pending and under consideration.

1. In view of the papers filed 8-1-03, the inventorship in this nonprovisional application has been changed by the deletion of Jamie L. Eberling.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 21-25 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delivering recombinant adeno-associated virus (rAAV) expressing aromatic amino acid decarboxylase (AADC) to monkey brain by intrastriatal administration of said rAAV via convection enhanced delivery, expression of AADC in striatum and conversion of L-dopa to dopamine in said striatum of monkey brain, does not reasonably provide enablement for a method of delivering a pharmaceutical composition comprising a rAAV expressing any therapeutic protein to the brain of a subject having central nervous system (CNS) disorder and the expression of said therapeutic protein provide a therapeutic effect for

various CNS disorders in said subject via various administration routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 1-27-03. Applicant's arguments filed 8-1-03 have been fully considered but they are not persuasive.

Applicants argue that considerable amount of routine experimentation is permitted and at the time of the invention, many CNS disorders and substances necessary to alleviate the disorders were known. Applicants cite declaration by Drs. Bankiewicz and Cunningham and argue that HSV-tk has been used to treat cancer and it was known that AADC was deficient in Parkinson's disease patient and one skilled in the art could readily determine the nucleotide sequences, the doses, the promoters, and the administration routes for treating various CNS disorders (amendment, p. 5, 6). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-27-03. The references cited in the declaration by Drs. Bankiewicz and Cunningham refer to the use of HSV-tk and GCV in killing tumor cells in vitro or via intratumoral injection in vivo. As discussed in the preceding Official action mailed 1-27-03, the state of the art for gene therapy was unpredictable at the time of the invention. One of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time". The administration route of the nucleotide sequence, fate of the DNA vector itself, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA

produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy in vivo. Therefore, each gene therapy protocol has to be considered individually because of the differences in the biological function of the proteins expressed, the administration routes, the diseases or disorders being treated, and the in vivo environments to reach the target cells. A success of one gene therapy protocol can not be extrapolated into success for another gene therapy protocol.

The scope of the claims is very broad and encompasses numerous CNS disorders, including migraine, Parkinson"s disease, Alzheimer's disease, glioma, neuroblastoma, multiple sclerosis, Huntington's disease, spinal cerebellar ataxia, schizophrenia etc. The specification fails to provide adequate guidance and evidence for how to deliver a pharmaceutical composition comprising a rAAV expressing any therapeutic protein to the brain of a subject such that expression of said therapeutic protein would provide therapeutic effect for various CNS disorders in a subject via various administration routes including CED. Although considerable amount of routine experimentation is permitted, however, in view of the reasons set forth above, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that the cited reference Deonarain has nothing to do with AAV-mediated gene therapy and Eck only devote a few paragraphs to AAV-mediated gene therapy. Applicants further argue that the problems cited in the references do not establish that applicants' specification is not enabling and the specification demonstrates effective delivery of rAAV virions for the treatment of Parkinsons's disease, and a myriad of post-filing publications

demonstrate universal applicability of the use of AAV-mediated gene delivery to treat CNS disorders (amendment, p. 6, 7). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-27-03 and the reasons set forth above. As discussed before, the specification of the present invention only enables delivering recombinant adeno-associated virus (rAAV) expressing aromatic amino acid decarboxylase (AADC) to a monkey brain by intrastriatal administration of said rAAV via convection enhanced delivery and expression of AADC in striatum and conversion of L-dopa to dopamine in said striatum of monkey brain. The specification fails to provide sufficient enabling disclosure for the full scope of the invention claimed. The specification must provide sufficient enabling disclosure for the claimed invention at the time of the filing but fails to do so. Although reference Deonarain does not refer to AAV-mediated gene delivery, references Eck and Gorecki do discuss AAV-mediated gene delivery. The references cited by examiner, i.e. Deonarain, Exk, and Gorecki, provide a general view of the state of the art of gene therapy in vivo, which was unpredictable at the time of the invention. Thus, whether Deonarain refers to AAV-mediated gene delivery is irrelevant. In view of the reasons set forth in the preceding Official action mailed 1-27-03 and the reasons set forth above, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed. Claims 21-25 remain rejected under 35 U.S.C. 112 first paragraph.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claim 21 remains rejected under 35 U.S.C. 102(b) as being anticipated by Okada et al., 1996 (Gene Therapy, Vol. 3, p. 957-964) and is repeated for the reasons set forth in the preceding Official action mailed 1-27-03. Applicant's arguments filed 8-1-03 have been fully considered but they are not persuasive.

Applicants argue that Okada does not teach the widespread distribution of rAAV virions as claimed (amendment, p. 8). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-27-03. Okada teaches stereotactic delivery (intracerebrally) of AAV-tk-IRES-IL2 particles into the tumor in the brain of nude mice followed by administration of GCV and reports that IL-2 was produced in a dose-dependent manner and 35 fold reduction in the mean volume of the tumors as compared to controls. Since the specification fails to specifically define what the phrase "widespread distribution" means, the intracerebral delivery of AAV-tk-IRES-IL2 particles into the tumor in the brain is considered widespread distribution such that 35 fold reduction in the mean volume of the tumors has been achieved. Thus, claim 21 remains rejected under 35 U.S.C. 102(b) as being anticipated by Okada.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 21-24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Okada et al., 1996 (Gene Therapy, Vol. 3, p. 957-964) in view of John, P., 1995 (WO 95/34670) and Zhu et al., 1996 (Gene Therapy, Vol. 3, No. 6, p. 472-476) and is repeated for the reasons set forth in the preceding Official action mailed 1-27-03. Applicant's arguments filed 8-1-03 have been fully considered but they are not persuasive.

Applicants argue that Okada does not teach the widespread delivery of rAAV virions to the brain and Johnson only teach stereotactic injection and does not teach delivery of a therapeutic protein. Applicants further argue that Zhu relates to liposome-mediated delivery not viral-mediated gene therapy and there is no motivation to combine these references but a hindsight construction (amendment, p. 9, 10). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-27-03 and the reasons set forth above under 35 U.S.C. 102(b) rejection. The rebuttal regarding "widespread distribution" is as discussed above under 102(b) rejection. Johnson does teach a method for treating a neurodegenerative disorder comprising administering a therapeutically effective dose of a

recombinant AAV encoding an AADC, nerve growth factor, NT-3, or tyrosine hydroxylase etc., which are therapeutic proteins, to a host exhibiting said neurological disorder. Although Zhu does not specifically teach viral-mediated gene therapy, liposome-DNA complex is one delivery method for gene therapy in vivo and Okada and Johnson both teach using rAAV vector for the delivery of gene encoding therapeutic protein to the brain in vivo.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). According to the collective teachings of Okada, Johnson and Zhu, it would have been obvious for one of ordinary skill at the time of the invention to deliver the AAV-tk-IRES-IL2 particles to the brain as taught by Okada via the use of osmotic minipump as taught by Zhu because they both teach delivering DNA encoding therapeutic protein, i.e. HSV-tk, into the brain of an animal to inhibit tumor growth and osmotic minipump is an administration technique for gene delivery, thus, it would have been obvious for one of ordinary skill to use osmotic pump for AAV vector delivery. One having ordinary skill at the time the invention was made would have been motivated to do so in order to deliver AAV vector encoding a therapeutic protein to the brain of an animal to inhibit glioma tumor growth as taught by Okada or to treat various neurodegenerative disorder as taught by Johnson with reasonable expectation of success. Thus, claims 21-24 remain rejected under 35 U.S.C. 103(a).

Conclusion

No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.